

STATISTICAL ANALYSIS PLAN

**An Open-label, Single-arm, Phase 3 Study of Carfilzomib in Combination With
Dexamethasone in Subjects With Relapsed and Refractory Multiple Myeloma in
China**

Protocol Number: 20140242
Version: Version 3.0
Date: 31 October 2018
Authors: PPD [REDACTED]

NCT Number: NCT03029234
This NCT number has been applied to the document
for purposes of posting on clinicaltrials.gov

Table of Contents

Table of Abbreviations	4
1. Introduction	6
2. Objectives	6
2.1 Primary Objective	6
2.2 Secondary Objectives.....	6
2.3 Exploratory Objectives.....	7
3. Study Overview	7
3.1 Study Design	7
3.2 Sample Size	8
4. Study Endpoints and Covariates	9
4.1 Study Endpoints	9
4.1.1 Primary Efficacy Endpoint	9
4.1.2 Secondary Efficacy Endpoints.....	9
4.1.3 Exploratory Efficacy Endpoints.....	10
4.2 Planned Covariates	10
5. Hypotheses and/or Estimations.....	10
6. Definitions	11
7. Analysis Subsets	15
7.1 Safety Analysis Set.....	15
7.2 Per Protocol Set	15
7.3 Pharmacokinetic Concentration Analyses Set.....	16
7.4 Subgroup Analyses	17
8. Interim Analysis and Early Stopping Guidelines.....	17
9. Data Screening and Acceptance.....	17
9.1 General Principles	17
9.2 Data Handling and Electronic Transfer of Data	17
9.3 Handling of Missing and Incomplete Data	18
9.4 Detection of Bias	18
9.5 Outliers	19
9.6 Distributional Characteristics	19
9.7 Validation of Statistical Analyses.....	19
10. Statistical Methods of Analysis.....	19
10.1 General Principles	19
10.2 Subject Accountability	20
10.3 Important Protocol Deviations	20
10.4 Demographic and Baseline Characteristics.....	20

10.5	Efficacy Analyses	21
10.5.1	Analyses of Primary Efficacy Endpoint(s).....	23
10.5.2	Analyses of Secondary Efficacy Endpoint(s).....	23
10.5.3	Analyses of Exploratory Efficacy Endpoints	25
10.6	Safety Analyses.....	25
10.6.1	Adverse Events	25
10.6.2	Laboratory Test Results	26
10.6.3	Vital Signs.....	27
10.6.4	Electrocardiogram (ECG)	27
10.6.5	Exposure to Investigational Product	27
10.6.6	Prior Medication, Concomitant Medication and Anti- cancer Therapy	27
10.7	Pharmacokinetic Analysis.....	28
11.	Changes From Protocol-specified Analyses	28
12.	Literature Citations / References.....	29
13.	Prioritization of Analyses	30
14.	Data Not Covered by This Plan.....	30
15.	Appendices	31

List of Tables

Table 1. 95% CIs for Various Observed ORRs With Study Size of 120 Subjects	9
Table 2. Planned Carfilzomib Dose per Week 3	15
Table 3. Endpoint Summary Table.....	21
Table 4. Date of Progression or Censoring for Progression-free Survival	24

List of Figures

Figure 1. Study Design and Treatment Schema	8
---	---

List of Appendices

Appendix A. Handling of Dates, Incomplete Dates and Missing Dates for Adverse Events and Concomitant Medications ¹	32
--	----

Table of Abbreviations

Abbreviation	Definition
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC _{0-inf}	area under the curve extrapolated to infinity
AUC _{0-last}	area under the curve, from time 0 to the last concentration measured
AUC _{last}	area under the plasma concentration curve up to the last measurable concentration
BSA	body surface area
CBR	clinical benefit rate
CFZ	carfilzomib [brand name: Kyprolis® (carfilzomib) for Injection]
CI	confidence interval
CL	total plasma clearance
C _{max}	maximum observed plasma concentration
CR	complete response
CRF	case report form
CrCl	creatinine clearance
DOR	duration of response
DCB	duration of clinical benefit
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EOT	End of Treatment
FISH	fluorescent in situ hybridization
H _A	alternative hypothesis
H ₀	null hypothesis
ICF	informed consent form
IMiD	immunomodulatory drug (thalidomide, lenalidomide or pomalidomide)
IMWG	International Myeloma Working Group
IMWG-URC	International Myeloma Working Group Uniform Response Criteria
IP	investigational product
IRC	Independent Review Committee
Kd	carfilzomib in combination with dexamethasone
MedDRA	Medical Dictionary for Regulatory Activities
MR	minimal response
MRT	mean residence time

Abbreviation	Definition
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
SAE	serious adverse event
SAP	Statistical Analysis Plan
sCR	stringent complete response
SFLC	serum-free light chain
SIFE	serum immunofixation electrophoresis
SPEP	serum protein electrophoresis
$T_{1/2}$	terminal elimination half-life or half-life
T_{max}	time to maximum plasma concentration
TTR	time to response
UIFE	urine immunofixation electrophoresis
ULN	upper limit of the normal
UPEP	urine protein electrophoresis
V_{area}	volume of distribution
V_{ss}	volume of distribution at steady state
VGPR	very good partial response
WBC	white blood cell

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol **amendment 3, superseding amendment 1.0** for study 20140242 carfilzomib, dated **12 April 2018**. The scope of this plan includes the primary analysis final analysis and long-term follow-up analysis that are planned and will be executed by the Biostatistics department unless otherwise specified. **Standard pharmacokinetic (PK) tables, figures and listings will be provided by the Clinical Pharmacology, Modeling and Simulation group.**

2. Objectives

2.1 Primary Objective

The primary objective of this study is to evaluate the overall response rate (ORR) after at least 6 cycles of carfilzomib in combination with dexamethasone (Kd) in subjects with multiple myeloma who have previously received an alkylating or anthracycline, bortezomib and an IMiD, have relapsed after 2 or more lines of therapy, and are refractory to the most recently received therapy.

ORR is defined as the proportion of subjects with a best overall response of sCR, CR, VGPR, or PR among all enrolled subjects with at least one dose of carfilzomib. ORR will be determined using best overall response as assessed by the Independent Review Committee (IRC) per IMWG-URC criteria (Protocol Appendix E). ORR will be analyzed when all the enrolled subjects have had the opportunity to be treated with at least 6 cycles of Kd and all the response assessments by the data cut-off date will be used.

2.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate ORR after at least 6 cycles of Kd using investigator assessment of response
- To evaluate ORR after at least 12 cycles of Kd
- To estimate Clinical Benefit Rate (CBR, defined as the proportion of subjects with a best overall response of MR or better) after at least 6 cycles and after at least 12 cycles
- To estimate Duration of Response (DOR)
- To estimate Duration of Clinical Benefit (DCB)
- To estimate Progression Free Survival (PFS)
- To estimate Overall Survival (OS)
- To estimate time to response (TTR)
- To characterize pharmacokinetics (PK) in a subset of subjects

2.3 Exploratory Objectives

A validated computer algorithm (Onyx Response Computational Assessment; [ORCA]) can be used to determine response and disease progression.

The exploratory objectives of this study are:

- To evaluate ORR after at least 6 cycles of Kd using ORCA assessment of response
- To evaluate ORR after at least 12 cycles of Kd using ORCA assessment of response
- To estimate CBR after at least 6 and after at least 12 cycles of Kd using ORCA
- To estimate DOR, DCB, PFS and TTR using ORCA

3. Study Overview

3.1 Study Design

This Phase 3 study will be conducted as a multicenter, open-label, single-arm study at approximately 15 centers in China. The study is designed to evaluate the efficacy and safety of carfilzomib in combination with low dose dexamethasone in subjects with multiple myeloma who have previously received an alkylating agent or anthracycline, bortezomib and an IMiD, relapsed following 2 or more therapies, and are refractory to the most recently received therapy.

Treatment cycles are every 28 days. In Cycle 1, subjects will receive carfilzomib 20 mg/m² infusion on Days 1 and 2. If well tolerated, the dose will escalate to 27 mg/m² to be given Cycle 1 Day 8 and onward.

Dexamethasone 20 mg will be given to subjects on Days 1, 2, 8, 9, 15, 16, 22, and 23 on a schedule of every 28 days. On days when carfilzomib is administered, the dexamethasone is to be given 30 minutes to 4 hours prior to carfilzomib.

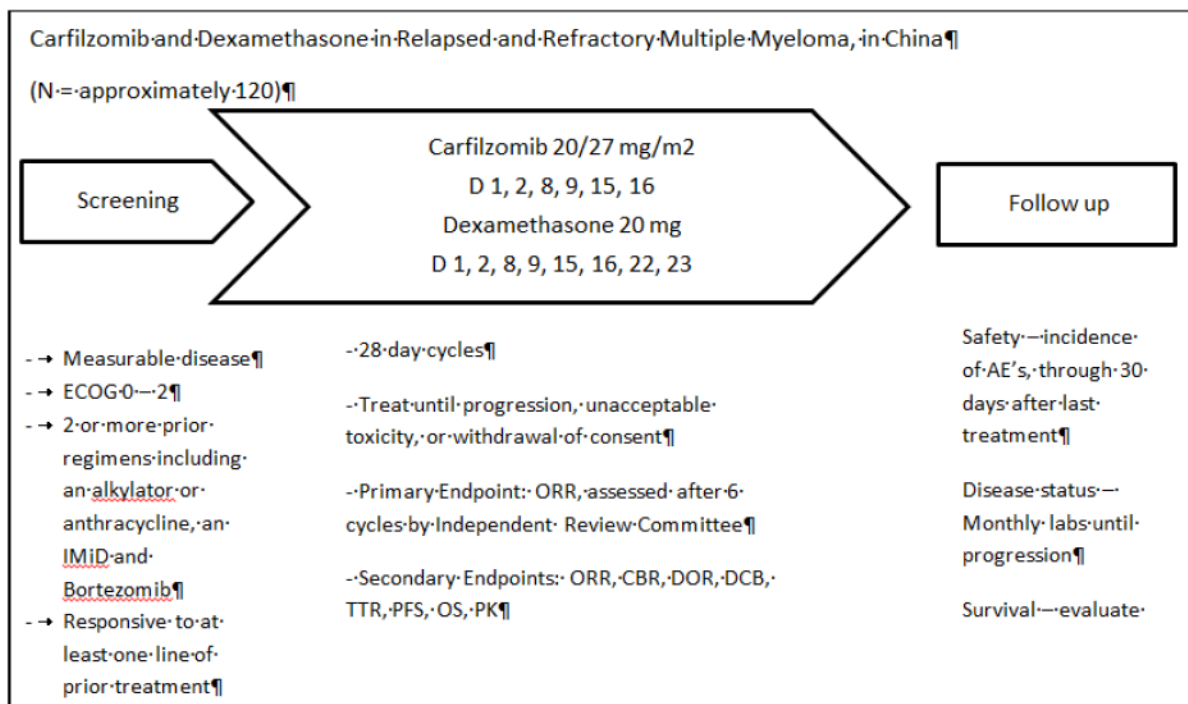
Subjects will receive treatment until disease progression, unacceptable toxicity, or discontinuation of study treatment for any other reason, whichever occurs first.

Dose reduction of carfilzomib and dexamethasone will be permitted per protocol guidelines (see protocol section 8.2).

Pharmacokinetic analyses will be characterized in a subset of approximately 15 subjects at selected sites. Subjects who do not provide all required PK assessments at Cycle 1 Day 1 and Cycle 2 Day 1 will be replaced.

The design schema for this open-label, single-arm study is presented in [Figure 1](#).

Figure 1. Study Design and Treatment Schema



Abbreviations: CBR = clinical benefit rate; DOR = duration of response; DCB = duration of clinical benefit; ECOG = Eastern Cooperative Oncology Group Performance Status; IMiD = immunomodulatory drug; N = number; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic(s); TTR = Time to Response

3.2 Sample Size

CCI

[Redacted]

This study will enroll approximately 120 subjects with relapsed and refractory multiple myeloma. CCI

CCI

[Redacted]

CCI

4. Study Endpoints and Covariates

4.1 Study Endpoints

4.1.1 Primary Efficacy Endpoint

The primary endpoint of this study is:

- ORR after at least 6 cycles of Kd based on best response assessment by IRC. The ORR is defined as the proportion of subjects with a best overall response of sCR, CR, VGPR, or PR per IMWG-URC criteria (Protocol Appendix E). ORR will be analyzed when all the enrolled subjects have had the opportunity to be treated with at least 6 cycles of Kd and all the response assessments by the primary analysis data cut-off date will be used.

4.1.2 Secondary Efficacy Endpoints

The secondary endpoints of this study are:

- ORR after at least 6 cycles of Kd based on response assessed by the investigator
- ORR after at least 12 cycles of Kd based on response assessed by both investigator and IRC, respectively. ORR will be analyzed when all the enrolled subjects have had the opportunity to be treated with at least 12 cycles of Kd and all the response assessments by the final analysis data cut-off date will be used.
- CBR after at least 6 cycles and after at least 12 cycles, based on response assessed by both investigator and IRC, respectively. Clinical benefit rate is defined as the proportion of subjects with the best overall response of MR or better per IMWG-URC criteria (Protocol Appendix E and F).

- Duration of response, defined as the time from first evidence of PR or better to disease progression or death due to any cause based on response assessed by both investigator and IRC, respectively
- Duration of clinical benefit, defined as the time from first evidence of MR or better to disease progression or death due to any cause based on response assessed by both investigator and IRC, respectively
- Progression-free survival, defined as the time from first dose of any study treatment to the earlier of disease progression or death due to any cause based on response assessed by both investigator and IRC, respectively
- Overall survival, defined as the time from first dose of any study treatment to the date of death due to any cause
- Time to response, defined as the time from first dose of any study treatment to the first confirmed response (PR or better) based on response assessed by both investigator and IRC, respectively
- Pharmacokinetics of carfilzomib

4.1.3 Exploratory Efficacy Endpoints

The exploratory endpoints of this study are:

- **ORR after at least 6 cycles of Kd using ORCA assessment of response**
- **ORR after at least 12 cycles of Kd using ORCA assessment of response**
- **CBR after at least 6 and after at least 12 cycles of Kd using ORCA**
- **DOR, DCB, PFS and TTR using ORCA**

4.2 Planned Covariates

Not Applicable.

5. Hypotheses and/or Estimations

The null (H_0) and the alternative (H_A) hypotheses are as follows:

$$H_0: \text{ORR}_{Kd} \leq 18\%$$

$$H_A: \text{ORR}_{Kd} > 18\%$$

This study will enroll approximately 120 subjects with relapsed and refractory multiple myeloma. The null hypothesis will be rejected and the study will be considered successful with the lower bound of the 2-sided 95% exact binomial CI about the overall response rate endpoint exceeding 18%.

6. Definitions

- Study treatment

Carfilzomib 20mg/m² IV on Day 1 and 2 of Cycle 1, escalating (if tolerated) to 27mg/m² on Day 8, 9, 15 and 16 of Cycle 1, and onward. Treatment cycles are 28 days.

Dexamethasone 20 mg on Day 1, 2, 8, 9, 15, 16, 22 and 23 on a schedule of every 28 days.

- Study baseline

Study baseline is defined as the value taken on Day 1 Cycle 1 before start of the first dose of any study treatment. If such value is not available it may be replaced by the latest available result taken before start of the first dose of any study treatment during the study.

- Study Day 1

Day 1 is defined as the day of treatment start, which is equal to the day of the first dose of any study treatment.

- Study Day

Study day represents the elapsed number of days from Study Day 1, inclusive.

$$\text{Study day } n = (\text{Date of assessment} - \text{Date of Study Day 1}) + 1$$

Unless otherwise specified, the timing of all study-related visits, assessments, and interventions will be calculated relative to Study Day 1. Study Day -1 will be the day before Study Day 1, and in general, negative days will be measured backwards starting from Study Day -1.

- Treatment period

Subjects will receive treatment until disease progression, unacceptable toxicity, or discontinuation of study treatment for any other reason.

- End of Treatment (EOT)

Patients may withdraw from study treatment at any time. Reasons for discontinuation include: decision by sponsor, completed, lost to follow-up, death, non-compliance, adverse event, pregnancy, withdrawal by subject and progressive disease. The End of Treatment assessments must be completed within 30 days of treatment discontinuation and prior to initiation of any new anti-myeloma therapy.

- Active Follow up

All subjects who discontinue study treatment for reasons other than PD will be followed in active follow-up every 4 weeks (**± 4 days; first visit should be 4 weeks after EOT visit**) for disease progression until confirmed PD, withdrawal of consent, loss to follow-up, **initiation of new, non-protocol anti-myeloma therapy**, death or

study closure. **Physical and laboratory assessments will be performed as clinically indicated.**

- Long Term Follow up

After disease progression **or initiation of new non-protocol anti-myeloma therapy**, subjects will be followed every 3 months (± 2 weeks) for survival for up to 3 years from initiation of study treatment, or until the subject has withdrawn consent, is lost to follow up, has died, or the sponsor makes the decision to close the study.

- End of Study

The time when the last subject completes 3 years of monitoring after initiation of study treatment **or when all subjects have withdrawn consent or died, whichever occurs first.**

- Primary Analysis

Primary analysis will be performed when all of the enrolled subjects have received at least 6 cycles of Kd or have discontinued treatment with Kd. All data by the primary analysis data cut-off date will be used.

- Final Analysis

Final analysis will be performed when all of the enrolled subjects have had the opportunity to be treated with at least 12 cycles of Kd or have discontinued treatment with Kd. All data by the final analysis data cut-off date will be used.

- Long Term Follow-up Analysis

Long term follow-up analysis will be performed when all of the enrolled subjects have been followed up for OS for up to 3 years from the start of their study treatment, or withdraw from further participation, is lost to follow-up, has died, or the sponsor makes a decision to close the study. All exposure and safety data by long term follow-up data cut-off date will be used.

- Best Overall Response

Best overall response is the best confirmed response by the data cutoff. The response assessments done after initiation of new anti-cancer therapy will be excluded from the evaluation of best overall response.

A confirmed response of minimal response (MR) or better requires at least two consecutive assessments with the same response or better. Progressive disease (PD) requires two consecutive PD assessments based on the same analyte except when PD is due to any of the following criteria:

- Definite development of new bone lesions or definite increase in the size of existing bone lesions
- Definite increase or new appearance of soft tissue plasmacytomas
- Definite increase of % plasma cells in bone marrow.

Best overall response will be decided in the following order of confirmed responses: stringent complete response (sCR), complete response (CR), very good partial

response (VGPR), partial response (PR), MR, SD, PD starting from the best to the worst.

- Treatment emergent adverse event (TEAE)

TEAEs are defined as those, which start between the first dose of any study treatment and 30 days after the end of study treatment, **or initiation of new anti-myeloma therapy, whichever comes first**. In case the start time or the exact start date of the AE is not available and it is thus unclear, whether an AE started after start of any study treatment or before 30 days after the end of treatment, the AE will be included in the analysis as TEAE.

- Time (months) from initial multiple myeloma diagnosis to study day 1

Defined as (study day 1 – initial diagnosis date +1)/30.4

- Time (months) from last relapse to study day 1

Defined as (study day 1 – last relapse date +1)/30.4

- Calculated ISS stage at baseline (stage I, stage II, stage III)

If $\beta 2$ -microglobulin level $< 3.5 \text{ mg/L}$ and albumin level $\geq 3.5 \text{ g/dL}$, the subject is at ISS stage I. If $\beta 2$ -microglobulin level $> 5.5 \text{ mg/L}$, the subject is at ISS stage III. If the subject is neither at stage I or stage III, then the subject is at ISS stage II.

- Risk group by FISH (high-risk group, standard-risk group)

High-risk group consists of subjects who have the genetic subtypes $t(4;14)$, $t(14;16)$, or $\text{del}(17p)$; standard-risk group consists of subjects who do not have any of the above genetic subtypes

- Refractory to prior multiple myeloma therapy

Subject is refractory to a drug received in prior regimens if the data collected on prior multiple myeloma therapy CRF indicates that any of the following criteria is met:

- Best Response to any regimen containing the drug is stable disease or progressive disease
- Reason the drug was stopped is progression in any regimen
- Date of relapse/progression is after start date and within 60 days after stop date of the drug in any regimen

- Cumulative Dose of Study Treatment

Carfilzomib:

Cumulative dose will be calculated in mg and mg/m^2 . The cumulative dose in mg will be calculated as the summation of total quantity administered (mg) over infusions. The cumulative dose in mg/m^2 will be calculated as the following over infusions.

$$\sum \frac{\text{Total quantity administered (mg)}}{\text{BSA (m}^2\text{)}}$$

BSA is to be determined by a standard formula, such as the Mosteller Formula (Mosteller 1987): body surface area (BSA) (m^2) = ([Height (cm) × Weight (kg)]/3600)^½. The one collected on cycle 1 day 1 will be used in the calculation till when BSA changes $\geq 20\%$ from cycle 1 day 1. Every time BSA changes $\geq 20\%$ from current BSA used in the calculation, the new BSA will be used for subsequent infusions. If BSA is > 2.2 , then 2.2 will be used in the calculation.

Dexamethasone:

The cumulative dose in mg will be calculated as the summation of total quantity administered (mg) over the study.

- **Relative Dose Intensity (RDI)**

RDI reflects whether the dose intensity of a therapy was implemented as planned. It will be calculated as the ratio of actual dose intensity relative to planned dose intensity.

$$\text{Relative Dose Intensity (\%)} = 100 \times \frac{\text{Actual Dose Intensity}}{\text{Planned Dose Intensity}}$$

Carfilzomib: Actual dose intensity is defined as the actual amount of drug in mg/m^2 delivered to a subject per week of treatment.

$$\text{Actual Dose Intensity (mg/m}^2\text{/week)} = \frac{\text{Cumulative Dose of Carfilzomib (mg/m}^2\text{)}}{\text{Number of Weeks of Actual Treatment}}$$

Cumulative dose of carfilzomib in mg/m^2 is defined before. Number of weeks of actual treatment will be calculated as (Last Dose Date of Carfilzomib – First Dose Date of Carfilzomib + i)/7, where i=7 if the last infusion is given on day 1 or 8 within the last cycle, i=6 if the last infusion is given on day 2 or 9, i=14 if the last infusion is given on day 15, i=13 if the last infusion is given on day 16.

Planned dose intensity is defined as the planned amount of carfilzomib in mg/m^2 delivered to a subject per week of treatment.

$$\begin{aligned} &\text{Planned Dose Intensity (mg/m}^2\text{/week)} \\ &= \frac{\text{Planned cumulative Dose of Carfilzomib (mg/m}^2\text{)}}{\text{Number of protocol specified treatment weeks}} \end{aligned}$$

It will be calculated as the planned cumulative dose of carfilzomib in mg/m^2 divided by the planned number of weeks for the treatment per protocol based on the corresponding cycle and day of the last carfilzomib infusion. Per protocol, one cycle is 28 days (4 weeks), so the planned number of treatment weeks will be calculated as $4 \times (c-1) + j$, where c is the cycle in which the last carfilzomib infusion is given and j=1 if the last carfilzomib infusion is given on day 1 or 2 within the last cycle, j=2 if the last infusion is given on day 8 or 9, j=4 if the last infusion is given on day 15 or 16. The planned cumulative dose of carfilzomib is the summation of planned carfilzomib dose per week as specified in [Table 2](#) across the planned treatment weeks.

Table 2. Planned Carfilzomib Dose per Week 3

Cycle	Week	Protocol Specified Dose for Treatment Week (mg/m²)
1	1 st	40
2 or later	1 st	54
All cycles	2 nd , 3 rd	54
All cycles	4 th	0

Dexamethasone: Actual dose intensity is the actual amount of drug in mg delivered to a subject per week of treatment.

$$\text{Actual Dose Intensity (mg/week)} = \frac{\text{Cumulative Dose of Dexamethasone (mg)}}{\text{Number of Weeks of Actual Treatment}}$$

Cumulative dose of dexamethasone in mg is defined before. Number of weeks of actual treatment will be calculated as (Last Dose Date of Dexamethasone – First Dose Date of Dexamethasone + i)/7, where i=7 if the last dexamethasone dose is given on day 1, 8, 15, and 22, i=6 if the last dexamethasone dose is given on day 2, 9, and 16 or 23.

Planned dose intensity (mg/week) is defined as the planned amount of dexamethasone in mg delivered to a subject per week of treatment. It will be 40 mg/week for dexamethasone.

7. Analysis Subsets

7.1 Safety Analysis Set

The safety analysis set is defined as all enrolled subjects who received at least one dose of carfilzomib. **This definition is in line with the intent-to-treat (ITT) principle in single-arm open-label studies. All safety analyses and efficacy analyses will be based on the safety analysis set.**

7.2 Per Protocol Set

The per-protocol set is defined as all enrolled subjects who received at least one dose of carfilzomib and didn't have any important protocol deviations (IPD) that might impact the efficacy evaluation of the subject.

Subjects with IPDs in the following list of IPD codes will be excluded from the per protocol set:

- IPD 101: Inclusion criteria of multiple myeloma
- IPD 102: Subjects must have measurable disease
- IPD 103: Subjects must have been responsive (i.e., achieved a MR or better) to at least 1 prior treatment regimens
- IPD 104: Refractory to the most recently received therapy
- IPD 105: Subjects must have ≥ 2 prior regimens
- IPD 106: Subjects must have received prior treatment with bortezomib and an IMiD
- IPD 204: Glucocorticoid therapy (prednisone > 10 mg/day or equivalent) within 3 weeks prior to Cycle 1 Day 1
- IPD 207: Chemotherapy with approved or investigative anticancer therapeutics including steroid therapy within the 3 weeks prior to Cycle 1 Day 1
- IPD 208: Radiation therapy or immunotherapy in the 4 weeks prior to Cycle 1 Day 1; localized radiation therapy within 1 week prior to Cycle 1 Day 1
- IPD 216: Non-hematologic malignancy within the past 3 years
- IPD 404: Subject required the use of excluded concomitant medication or procedure while on study and was not withdrawn from study treatment
- IPD 801: Subject ended treatment without confirmation of PD for reason other than progressive disease or intolerability to treatment and no further disease assessments were carried out
- IPD 804: Any baseline disease assessments not done in such a way that patient is not measurable as defined per protocol

A sensitivity analysis based on this per protocol set will be performed for the primary endpoint and secondary efficacy endpoints based on IRC assessment as well as OS (see [Table 3](#)).

7.3 Pharmacokinetic Concentration Analyses Set

The pharmacokinetic (PK) concentration analysis set will contain all subjects who received carfilzomib given as a 30 ± 2 minutes IV infusion, and have adequate carfilzomib plasma concentration versus time data for the estimation of PK parameters by a noncompartmental analysis.

7.4 Subgroup Analyses

Subgroup analyses will be performed to examine the consistency of the treatment effect for the primary endpoint and key secondary efficacy endpoints (ORR after at least 12 cycles of Kd per IRC, PFS per IRC and OS) which will be based on the following factors:

- Sex (male vs. female)
- Age (as categorical variable: 18-< 65, 65-< 75, ≥ 75 years)
- Baseline ECOG performance status (0, 1-2)
- Baseline creatinine clearance (< 50, 50-< 80, ≥ 80 mL/min)
- Baseline corrected calcium (≤11.5, > 11.5 mg/dL)
- ISS stage at baseline (stage I, stage II, stage III)
- ISS stage at diagnosis (stage I, stage II, stage III, Unknown)
- β2-microglobulin level (< 3.5, ≥ 3.5 and < 5.5, ≥ 5.5 mg/L)
- Number of prior regimens: (2, 3, 4, ≥ 5)
- Prior transplant (yes, no)
- Bortezomib (BTZ), or Ixazomib refractory to any prior line regimen (yes, no)
- IMiD refractory to any prior line regimen (yes, no)
- Both Proteasome inhibitor [Bortezomib (BTZ), or Ixazomib] and IMiD refractory to any prior line regimen (yes, no)

These subgroups will be re-examined and appropriately re-categorized before database snapshot or lock for primary analysis. Subgroup analysis containing a subgroup of less than 10% of the whole population will not be conducted **or will be re-categorized if it is proper.**

8. Interim Analysis and Early Stopping Guidelines

Not Applicable.

9. Data Screening and Acceptance

9.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

9.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database.

An Analysis Dataset for PK Concentrations (ADPC) will be provided to the appropriate CPMS representative from Global Biostatistical Science.

9.3 Handling of Missing and Incomplete Data

In general, missing data will not be imputed unless otherwise specified. For the primary endpoint ORR, patients without post-baseline response data will be considered as non-responders. The endpoint-specific rules on missing data are described in [Section 10.5](#). Data will be analyzed as retrieved from the database provided by CDM except for analyses requiring imputations. The imputed data will be written to the derived datasets but not to the raw data. The imputation algorithm will be described in the Data Definition Table (DDT).

The handling of incomplete and partial dates for adverse events and concomitant medications are described in [Appendix A](#).

If the start day of new anti-cancer therapy is missing and month and year are not same as last dosing date of study treatment, it will be assumed to be the first day of the month.

If the start day of new anti-cancer therapy is missing and month and year are same as last dosing date of study treatment, and the subject does not have protocol deviation of using excluded procedure while on study, the start date will be assumed as last dose date of study treatment plus 1 day. In other situation, do not impute it.

If the day of initial diagnosis is missing and month and year are present, impute 15 for the day. For other cases, do not impute.

If only the day of a death date is missing, the death will be assumed to be on the first day of the month if the last known alive date is earlier. If the last known alive date is later than the first day of the month, then the death date will be assumed to be the last known alive date plus 1 day.

PK concentrations that are below the quantification limits will be set to zero when engaging non-compartmental model to compute PK parameters.

9.4 Detection of Bias

The sources of possible bias will be summarized and be considered while interpreting study results. Sources of bias to be considered may include protocol violations or informative censoring.

9.5 Outliers

Any suspected outliers will be investigated by the study team and will be included in the database unless determined to be an error or there is supporting evidence or explanation to justify the exclusion. Any outliers excluded from the analysis will be discussed in the Clinical Study Report (CSR), including the reasons for exclusion and the impact of their exclusion on the study.

PK concentration data will be evaluated for outliers by visual inspection, and decisions to re-assay individual samples will be made in accordance with standard pharmacokinetic evaluation practice.

9.6 Distributional Characteristics

Not Applicable.

9.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later for analysis except PK/PD.

10. Statistical Methods of Analysis

10.1 General Principles

For categorical variables, the frequency and percentage in each category will be presented. Point estimates for categorical efficacy endpoints will be accompanied by 2-sided 95% exact binomial confidence interval.

For continuous variables, the number of subjects with non-missing data (N), mean, standard deviation (SD), median, 25th percentile, 75th percentile, minimum and maximum will be presented.

For time-to-event endpoints, the distribution and percentiles will be estimated by Kaplan-Meier (KM) method and their 95% confidence intervals (CI) will be provided utilizing the [Brookmeyer and Crowley \(1982\)](#) method with log-log transformation.

10.2 Subject Accountability

The number and percent of subjects who were enrolled, received carfilzomib as well as dexamethasone, were still on treatment, discontinued carfilzomib along with the reasons and discontinued study along with the reasons will be summarized.

The number and percent of enrolled subjects will be tabulated by study site. Key study dates for the first subject enrolled, last subject enrolled, and data cut-off date for analysis will be presented.

10.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's first visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, sub-category codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol.

The number and percent of subjects with the important protocol deviations will be summarized by the IPD category and sub-category and also be listed.

10.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized using descriptive statistics for the safety analysis set:

- Age (years),
- Age group (18-< 65, 65-< 75, \geq 75 years),
- sex (Female, Male)
- ECOG (0, 1, 2)
- height
- weight
- body surface area (m²)
- Time (months) from initial multiple myeloma diagnosis to study Day 1
- Time (months) from last relapse to study Day 1
- Baseline laboratories including: **hemoglobin(for male: <120 g/L, \geq 120 g/L; for female: < 110 g/L, \geq 110 g/L)**, ANC level (< $1.5 \times 10^9/L$, $\geq 1.5 \times 10^9/L$), platelet count level (< $150 \times 10^9/L$, $\geq 150 \times 10^9/L$), creatinine clearance (< 30, 30-< 50, 50-< 80, \geq 80 mL/min)
- Baseline LVEF (%)
- ISS stage at baseline (stage I, stage II, stage III)
- ISS stage at diagnosis (stage I, stage II, stage III)
- Number of prior regimens: (2, 3, 4, \geq 5)

- β 2-microglobulin level at baseline (< 3.5 , $3.5- < 5.5$, ≥ 5.5 mg/L)
- Determination of measurable disease (SPEP, UPEP, **both SPEP and UPEP**, sFLC)
- M-protein heavy and light chain subtype
- Serum free light chain Kappa/Lambda ratio
- Presence of plasmacytoma (yes, no)
- Presence of bone lesions (yes, no)
- Corrected calcium at baseline (≤ 11.5 , > 11.5 mg/dL)
- Refractory to PI [either bortezomib (BTZ), **or ixazomib**] in any prior line regimen (yes, no)
- Refractory to IMiD in any prior line regimen (yes, no)
- Refractory to both **PI [Bortezomib (BTZ), or ixazomib]** and IMiD in any prior line regimen (yes, no)
- Prior transplant (yes, no)
- Prior surgery (yes, no)
- Prior radiotherapy (yes, no)

10.5 Efficacy Analyses

A table summarizing the efficacy endpoints and planned analysis methods is provided below ([Table 3](#)) for the primary and key secondary endpoints. Exploratory endpoints will also be analyzed per **methods** in [Table 3](#).

Table 3. Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method
Primary Endpoint	
ORR after at least 6 cycles of Kd based on IRC response assessment	<ul style="list-style-type: none"> • Estimate along with the corresponding 95% exact binomial CI in the safety analysis set. • The null hypothesis will be rejected and the study will be considered successful with the lower boundary of the 2-sided 95% exact binomial CI exceeding 18%. IRC response assessment data will be used. • The sensitivity analysis will be performed using the per protocol set.
Secondary Efficacy Endpoints	
ORR after at least 6 cycles of Kd based on Investigator's response assessment	<ul style="list-style-type: none"> • Estimate along with the corresponding 95% exact binomial CI in the safety analysis set. • Investigator's response assessment data will be used.

Table 3. Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method
Secondary Efficacy Endpoints (continued)	
ORR after at least 12 cycles of Kd based on IRC and investigator's response assessment	<ul style="list-style-type: none"> Estimate along with the corresponding 95% exact binomial CI in the safety analysis set. IRC and Investigator's response assessment data will be used respectively. This analysis will be only performed at final analysis. The sensitivity analysis will be performed using the per protocol set for IRC assessment.
CBR after at least 6 and at least 12 cycles of Kd based on IRC and investigator's response assessment	<ul style="list-style-type: none"> Estimate along with the corresponding 95% exact binomial CI in the safety analysis set. IRC and Investigator's response assessment data will be used respectively. CBR after 12 cycles will only be performed at final analysis. The sensitivity analysis will be performed using the per protocol set for IRC assessment.
DOR based on IRC and investigator's response assessment	<ul style="list-style-type: none"> As time-to-event endpoint, median and other percentile estimate using K-M curve and 95% CI using Brookmeyer and Crowley (1982) method. Subjects who achieved PR or better are included according to IMWG-URC criteria. IRC and Investigator's response assessment data will be used respectively. The sensitivity analysis will be performed using the per protocol set for IRC assessment.
DCB based on IRC and investigator's response assessment	<ul style="list-style-type: none"> As time-to-event endpoint, median and other percentile estimate using K-M curve and 95% CI using Brookmeyer and Crowley (1982) method Subjects who achieved MR or better are included per IMWG-URC criteria. IRC and Investigator's response assessment data will be used respectively. The sensitivity analysis will be performed using the per protocol set for IRC assessment.
PFS based on IRC and investigator's response assessment	<ul style="list-style-type: none"> As time-to-event endpoint, median and other percentile estimate using K-M curve and 95% CI using Brookmeyer and Crowley (1982) method in the safety analysis set IRC and Investigator's response assessment data will be used respectively. The sensitivity analysis will be performed using the per protocol set for IRC assessment.
OS	<ul style="list-style-type: none"> As time-to-event endpoint, median and other percentile estimation using K-M curve and 95% CI using Brookmeyer and Crowley (1982) method in the safety analysis set The sensitivity analysis will be performed using the per protocol set.

10.5.1 Analyses of Primary Efficacy Endpoint(s)

Overall response rate, defined as the proportion of subjects with the best overall response of PR or better, will be estimated along with corresponding 95% exact binomial CI. ORR will be analyzed when all the enrolled subjects have had the opportunity to be treated with at least 6 cycles of Kd and all the response assessments by the data cut-off date will be used. Responses will be assessed by the IRC according to the IMWG-URC criteria (Protocol Appendix E). The primary analysis will be based on the safety analysis set. Summary of responses status by each response category will be also provided.

10.5.2 Analyses of Secondary Efficacy Endpoint(s)

Overall Response Rate

Overall response rate (after at least 6 cycles of Kd), based on the investigator's assessment of best response according to IMWG-URC criteria will be estimated along with corresponding 95% exact binomial CI. The primary analysis will be based on the safety analysis set. Summary of other best responses status by each response category will be also provided.

Overall response rate (after at least 12 cycles of Kd), based on both IRC and investigator assessment of best overall response will be estimated along with the corresponding 95% exact binomial CI. Summary of other best responses status by each response category will be also provided. The discordance between results from IRC and the investigators will be summarized. This analysis will only be analyzed at final analysis when all the enrolled subjects have had the opportunity to be treated with at least 12 cycles of Kd and all the response assessments by the final analysis data cut-off date will be used.

The discordance between ORR results from IRC, investigators **and ORCA** will be summarized.

Clinical Benefit Rate (CBR)

Clinical benefit rate, defined as the proportion of subjects with the best overall response of MR or better, will be estimated along with the 95% exact binomial CI. Minimal response will be defined according to IMWG-URC criteria (Protocol Appendix F). Clinical benefit rate will be calculated after at least 6 and at least 12 cycles of Kd and determined by both investigator and IRC response assessments respectively.

Duration of Response (DOR)

Duration of response (DOR) is defined as the time from first evidence of PR or better to disease progression or death due to any cause. Duration of response will be determined based on both investigator and IRC response assessments respectively. Duration of response will be right-censored based on the censoring conventions defined in [Table 4](#) for PFS. The analysis of DOR will be carried out for the subjects in the safety analysis set who achieve PR or better according to IMWG-URC criteria.

Duration of Clinical Benefit (DCB)

Duration of clinical benefit (DCB) is defined as the time from first evidence of MR or better to disease progression or death due to any cause. Duration of clinical benefit will be right-censored based on the censoring conventions defined in [Table 4](#) for PFS. The analysis of DCB will be carried out for the subjects in the safety analysis set who achieve MR or better according to IMWG-URC criteria.

Progression-free Survival (PFS)

Progression-free survival (PFS) is defined as the time from first dose of any study treatment to the earlier of disease progression or death due to any cause. Progression-free survival will be determined based on both investigator and IRC response assessments. For purpose of calculating PFS, the start date for PD is the date at which progression is first observed. The duration of PFS will be right-censored for subjects who meet one of the following conditions described in [Table 4](#).

Table 4. Date of Progression or Censoring for Progression-free Survival

Situation	Date of Progression or Censoring	Outcome
No baseline disease assessments	Date of first dose	Censored
New anticancer therapy started before documentation of PD or death	Date of last disease assessment prior to start of new anticancer therapy	Censored
Death or PD immediately after more than 1 consecutively missed disease assessment visit	Date of last disease assessment visit without documentation of PD that is before the first missed visit	Censored
Alive and without PD documentation	Date of last disease assessment	Censored
Death or PD between planned disease assessments	Date of death or first disease assessment showing PD, whichever occurs first	Progressed
Death before first disease assessment	Date of death	Progressed

Overall Survival (OS)

Overall survival (OS) is defined as the time from the first dose of any study treatment to the date of death due to any cause. Subjects who are alive or lost to follow-up as of the data analysis cutoff date will be right-censored at the subject's date of last contact (last known to be alive).

Analyses for all time-to-event secondary endpoints (DOR, DCB, PFS, OS) will be performed using the Kaplan-Meier method, and calculated using both IRC and investigator response assessments respectively (except OS). Medians and other quartiles for each endpoint will be calculated with the corresponding two-sided 95% CI. Median follow-up for PFS and OS will also be estimated according to the Kaplan-Meier estimate of potential follow-up also termed "reverse Kaplan-Meier" ([Schemper 1996](#)).

Time to Response (TTR)

Time to response (TTR) is the time from the first dose of any study treatment to the first confirmed response (PR or better) and will be determined based on both investigator and IRC response assessments. The descriptive statistics including mean, standard deviation, median, minimum and maximum will be calculated. The analysis of TTR will be carried out for subjects in the safety analysis set who achieve at least a PR or better according to IMWG-URC criteria.

10.5.3 Analyses of Exploratory Efficacy Endpoints

ORR after at least 6 cycles and after at least 12 cycles of Kd, CBR after at least 6 and after at least 12 cycles of Kd, DOR, DCB, PFS and TTR determined by ORCA will be analyzed per the methods described in [Section 10.5.1](#) and [Section 10.5.2](#).

10.6 Safety Analyses

All safety analyses will be based on the safety analysis set.

10.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 or later will be used to code all adverse events (AE) to a system organ class and a preferred term. AEs of interest (EOI) categories will be based on search strategies defined by the EOI steering committee.

A subject reporting the same AE more than once will be counted only once when calculating 1) within a given system organ class and 2) within a given system organ class and preferred term combination. For such cases, the maximum NCI-CTCAE

toxicity grade and strongest causal relationship to investigational product for the event will be used in the incidence calculations.

The subject incidence of AEs will be summarized for all TEAEs, \geq grade 3 TEAEs, serious AEs, AEs leading to modification (ie, discontinuation, reduction, or interruption) of carfilzomib/dexamethasone, fatal AEs, treatment related AEs, treatment related SAEs, treatment related \geq grade 3 TEAEs by preferred term. Those AEs will also be summarized by system organ class and preferred term in descending order. **In addition, a summary of TEAEs will be tabulated by system organ class, preferred term, and worst grade based on NCI-CTCAE Version 4.03 or later version.**

AEs of interest (EOI), serious EOI, \geq grade 3 EOI, treatment related EOI, EOI leading to modification of carfilzomib will be tabulated by search strategy and preferred term in descending order of frequency. Subject incidence of EOIs will also be tabulated by worst grade **based on NCI-CTCAE version 4.03 or later version** in descending order of frequency.

Summaries of treatment-emergent AEs, serious AEs and EOIs occurring in at least 5% of the subjects will be provided by system organ class (or search strategy for EOI) and preferred term in descending order of frequency.

All deaths during treatment period (\leq 30 days of the last dose of study treatment, **or until new anti-myeloma therapy, whichever comes first**) and deaths beyond treatment period will be summarized along with the reason and also be listed regardless of whether due to AE or not.

All AEs will be included in individual subject listings.

10.6.2 Laboratory Test Results

Laboratory parameters including hematology and chemistry parameters will be summarized using descriptive statistics (mean, standard deviation, median, range) for each scheduled assessment time point. Changes and percent changes from study baseline will be descriptively summarized at each scheduled visit.

Laboratory test results will be assigned toxicity grades using the NCI Common Toxicity Criteria for Adverse Events (CTCAE). The subject incidence of Grade 3 and 4 laboratory toxicities will be provided. Shifts in laboratory toxicity grades to outside the normal range will be evaluated for selected laboratory parameters.

Subjects without a baseline and/or post-baseline value will be excluded. Subjects with missing data for a scheduled assessment time point will be excluded. **Laboratory values from unscheduled assessments will be excluded.** Laboratory results from samples taken **after new anti- myeloma therapy or > 30 days** after the last administration of study treatment will be excluded from all laboratory summaries.

10.6.3 Vital Signs

Vital sign results including blood pressure, heart rate, respiratory rate and temperature will be summarized descriptively for each scheduled protocol time point. Changes and the percent changes from study baseline will be descriptively summarized at each scheduled visit, minimum, maximum and last observed values.

Subjects without a baseline and/or post-baseline value will be excluded. Subjects with missing data for a scheduled assessment time point will be excluded. **Vital sign values from unscheduled assessments will be excluded.** Vital sign results **obtained after new anti-myeloma therapy or > 30 days** after the last administration of study treatment will be excluded.

10.6.4 Electrocardiogram (ECG)

The twelve-lead ECG measurements from this clinical study were required in all subjects at screening and at the end of treatment only. Because these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data, the analysis of ECGs will only involve descriptive statistics.

10.6.5 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product for subjects in the Safety Analysis Set. The number of cycles of protocol-specified therapy administered will be summarized with an additional breakdown of the number of cycles started. In addition, the duration of therapy, the cumulative dose, and the average dose per administration and relative dose intensity will be summarized for each drug. The number and percent of subjects with dose modifications (eg, dose reductions, dose interruptions) and reason for modification will be summarized.

10.6.6 Prior Medication, Concomitant Medication and Anti-cancer Therapy

Prior medications are defined as medication taken or administered prior to first dose of study treatment administration. Prior medications can be discontinued before the first dose of study treatment or can be continuing into the treatment period.

Concomitant medications are any medications received by the subject concomitantly to any study treatment, from first study treatment administration through 30 days after the last study treatment administration, **or initiation of new anti-myeloma therapy, whichever comes first.**

A given medication can be classified both as a prior medication and as a concomitant medication.

The number and proportion of subjects receiving prior and concomitant medications will be summarized by preferred term or category as coded by the World Health Organization Drug (WHO DRUG) dictionary.

Subjects who received anti-cancer therapy **during long term follow up** will be summarized.

10.7 Pharmacokinetic Analysis

Pharmacokinetic concentration analysis set will include subjects who received carfilzomib and had adequate carfilzomib plasma concentration versus time data for the estimation of PK parameters by a noncompartmental analysis.

Individual and mean plasma concentration versus time data will be tabulated and plotted for the subjects participating in the PK portion of the study. The following PK parameters will be determined when possible for carfilzomib:

- Maximum observed plasma concentration (C_{\max})
- Time of maximum observed plasma concentration (t_{\max})
- Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration and to infinity ($AUC_{0-\text{last}}$ and $AUC_{0-\text{inf}}$, respectively)
- Terminal elimination half-life ($t_{1/2}$)
- Systemic plasma clearance (CL)
- Volume of distribution (V_{area})
- Volume of distribution at steady state (V_{ss})
- Mean residence time (MRT)

All PK parameters will be computed using actual doses administered and actual elapsed time calculated relative to the start of dose administration.

Standard pharmacokinetic (PK) tables, figures and listings will be provided by Clinical Pharmacology, Modeling & Simulation.

11. Changes From Protocol-specified Analyses
Not Applicable.

12. Literature Citations / References

Brookmeyer, R. and Crowley, J. (1982) A Confidence Interval for the Median Survival Time, *Biometrics*, 38, 29 - 41.

Greipp, P. R., Miguel, J. S., Durie, B. G., Crowley, J. J., Barlogie, B., Bladé, J., ... & Lahuerta, J. J. (2005). International staging system for multiple myeloma. *Journal of clinical oncology*, 23(15), 3412-3420

Kumar, S., Paiva, B., Anderson, K. C., Durie, B., Landgren, O., Moreau, P., ... & Dimopoulos, M. (2016). International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *The Lancet Oncology*, 17(8), e328-e346.

Rajkumar, S. V., Harousseau, J. L., Durie, B., Anderson, K. C., Dimopoulos, M., Kyle, R., ... & Jagannath, S. (2011). Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood*, blood-2010.

Schemper M, Stare J. (1996) Explained variation in survival analysis. *Stat Med*. 15:1999–2012.

13. Prioritization of Analyses

Not Applicable.

14. Data Not Covered by This Plan

Not Applicable.

15. Appendices

Appendix A. Handling of Dates, Incomplete Dates and Missing Dates for Adverse Events and Concomitant Medications

The following data will be imputed using the following algorithm:

- Adverse Events
- Concomitant Medications

Imputation Rules for Partial or Missing Start Dates

Start Date		Stop Date						
		Complete: yyyymmdd		Partial: yyyymm		Partial: yyyy		missing
		< 1 st dose	≥ 1 st dose	< 1 st dose yyyymm	≥ 1 st dose yyyymm	< 1 st dose yyyy	≥ 1 st dose yyyy	
Partial: yyyymm	= 1 st dose yyyymm	2	1	2	1	n/a	1	1
	≠ 1 st dose yyyymm		2		2	2	2	
Partial: yyyy	= 1 st dose yyyy	3	1	3	1	n/a	1	1
	≠ 1 st dose yyyy		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute the date of first dose

2 = Impute the first day of the month

3 = Impute January 1 of the year

4 = Impute January 1 of the stop year

Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.

Imputation rules for partial or missing stop dates:

- For partial stop date mmyyyy, impute the last day of the month.
- For partial stop date yyyy, impute December 31 of the year.
- For completely missing stop date, do not impute.
- If the stop date imputation leads to a stop date that is after the death date, then impute the stop date as the death date.
- If the stop date imputation leads to a stop date that is before the start date, then there is a data error and do not impute the stop date. (ie, set the stop date as missing).